Impacts of the Exclusion of Gender as a Consideration in Healthcare Funding, Diagnosis, and Treatment

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia - Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

Gabrielle Hope Gilpin

Spring, 2024

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Advisors

William F. Stafford Jr., Department of Engineering and Society

Background

Healthcare is a case-study based discipline. Every day, clinicians make assumptions, generalizations, and decisions based on previously researched information and past experiences that they themselves have had or that they've read in a case-study written by another doctor who has encountered something similar. But what happens when that information isn't complete? When those assumptions, generalizations and decisions are used to guide life-impacting decisions without taking into consideration half the world's population? This exclusion of gender can date back to the third century BCE when women due to their anatomical and biological differences from men were "medically defined as faulty, defective, deficient" (*The Long History of Gender Bias in Medicine*, 2021). It has only been since 1985 that women were allowed to participate in clinical studies. Prior to that and explicitly in 1977, the Food and Drug Administration (FDA) released a policy that recommended "excluding women of childbearing potential from Phase I and early Phase II drug trials" ("History of women's participation in clinical research," n.d.) This included all women who had the capability to give birth, including those using contraception from all drug trials prior to 1985. It wasn't until almost ten years later in 1993 that the FDA clearly required studies to include female specimens - whether those specimens be cells, animals or humans - in research and clinical studies ("History of women's participation in clinical research," n.d.). That means that any research and discovery made before 1993 holds the assumption that the information gathered from only men applies equally to both men and women. That presumption leaves a massive gaping hole in the root of healthcare and because it isn't fixed, as current research continues, it builds additional assumptions off of these outdated generalizations.

Disregarding gender in medicine, healthcare, and research within the healthcare discipline has created a system that is male-centric. The system dismisses not just the obvious biological differences between men and women - disregarding differences in anatomy, hormones, genetics, and other biological pathways still unknown - but also the social differences that account for the different stressors men and women face on a daily basis. Despite these seemingly obvious differences between men and women, healthcare research and therefore treatment, pathology, and diagnosis do not largely distinguish between genders. The largest distinction made is simultaneously the largest generalization made - that men and women differ only based on their reproductive anatomy. Think about it yourself. When you think of women's health, what comes to mind? Obstetrics and gynecology. Breast cancer screening. Menstruation. Giving birth. Not the effect of every day drugs and medications on men versus women. Not the method of diagnosis of stroke in men versus women. Most probably don't consider that the very model in healthcare that is used to teach future clinicians is a high-tech mannequin that is male and white (McGregor, 2021, p. xii). What about the differences in hormonal cycles that men and women experience and how that affects their life each day?

Men's hormone levels are based on a 24-hour cycle. Their hormones and therefore their emotions, reactions, and moods fluctuate around the same time every day. They wake up feeling energized and go to bed feeling tired, feeling the benefits of any supplements or daily medications they take. Women follow a 28-day cycle, guided by their menstrual cycle. Hormone levels fluctuate throughout the span of a month. One day a woman can wake up and feel energized and motivated while the next week feel angry and tired from being kept awake because her cycle is causing pain and mood fluctuations (McGregor, 2021, p. 76). The differences and

effects of hormone cycles in men versus women and their effect on research was first recognized in the early 1970s as medical research progressed and clinical trials became more regulated. Researchers started to observe that the 28-day hormone cycle that women experience created deviations in their studies. Instead of looking closer at the differences, the researchers opted to omit women from their studies and assume that women and men would have the exact same pathologies (McGregor, 2021, p. 23). This single generalization had massive implications that are ongoing today, including unequal funding distribution by large public institutions, misdiagnosis of chronic diseases in women, and mistreatment of common medications and drugs to women. The generalization further led to a continuous lack of critical research that in turn perpetuates a cycle of ignorance, mistreatment of medication, and misdiagnosis of chronic diseases in women.

Before delving into the ramifications of neglecting gender in medicine, it's essential to recognize that the assertions and research within this paper simplify gender into heterosexual norms. This binary norm ignores the impact of healthcare on individuals identifying as transgender, nonbinary, and other gender identities. Furthermore, this paper does not address the implications of healthcare on race within its scope. The acknowledgement racial bias is crucial. As it has been established, the United States healthcare system was developed on the basis of being white and male, therefore creating additional biases in research, funding, diagnosis, and treatment for persons of other races and non-heterosexual gender identities. This is important to mention as the constraints of a paper does not allow the capacity to sufficiently address each of these excluded populations as well as how they connect to one another. Therefore, this paper aims to begin the

identification of exclusion within the healthcare system with the hope of it opening up further conversations.

Funding and its Influence on the Ignorance of the Healthcare System

Dr. Arthur Mirin is a mathematician who was directly affected by the exclusive tendencies of the U.S. healthcare system and decided to probe further to identify a source of this issue. Dr. Mirin began a deep dive into the distribution of funding in biomedical research after his daughter was diagnosed with myalgic encephalomyelitis (ME/CFS), also referred to as chronic fatigue syndrome. His daughter struggled to find viable treatment for her symptoms leading Dr.Mirin to investigate. The Centers for Disease Control and Prevention (CDC) estimates that between 836,000 and 2.5 million Americans are diagnosed with ME/CFS ("Epidemiology," 2023). Among the persons diagnosed with ME/CFS, the ratio of women diagnosed to men is 4 to 1 ("Epidemiology," 2023). In his study, Mirin used a metric called "disability-adjusted life years" (DALYs) to create a numerical value for the burden of disease. In 2022, the National Institute of Health (NIH) spent $45 billion on biomedical research ("Women's health research lacks funding - these charts show how," 2023). Of the diseases Mirin examined, he found that female-dominant diseases (having an affected population of over 60% women) attract much less funding in proportion to the burden felt by the US population. Mirin found that ME/CFS specifically had the lowest funding by the NIH of the diseases he studied relative to disease burden. The results of Mirin's study showed that of the diseases studied, in nearly 75% of diseases that primarily affect one gender, NIH funding shows a distinct pattern favoring males (Mirin, 2021). This means that of the diseases primarily affecting females, the ratio of burden to funding show that the diseases are underfunded and that of the diseases primarily affecting males are overfunded

for the burden inflicted on the US population. Mirin found these results from the 75 diseases that he examined. A chi-square test of this study yielded a p-value of 0.015, which shows that the results of this study are statistically likely to be representative of the entire NIH biomedical funding portfolio (Mirin, 2021).

The implications of this uneven funding distribution of biomedical research have implications that affect the entire healthcare system. According to this study, of 75% of diseases that primarily affect one gender, NIH funding tends to favor males. This funding pattern doesn't just affect women… It affects everyone. Uneven funding distribution like this means that there are a large number of diseases that, according to their burden, inflict a lot of people who should have access to a treatment that doesn't exist and to symptoms that don't have answers because resources aren't being equally put towards them. Less funding is less incentive for research as even if the disease and treatments are considered for investigation, fewer resources are available due to the minimal funding. In addition, "it is well recognized that physician-scientists are the driving force behind the research that will advance healthcare", but if those scientists and doctors aren't choosing to specialize in the areas that need it, necessary healthcare advancements will continue to slow (Rice et al., 2020). Clinicians are less motivated to specialize in areas that receive less funding not just because of limited access to resources compared to better funded research areas. The compensation in those areas is decreased, and they have less information to reference, making their lives more difficult. In 2018, the US Congress increased funding to the NIH, however obstetrics and gynecology (OBGYN) for example received only 1% of the $14.3 billion in funding. Approximately 4% of all trainees in healthcare specialize in OBGYN, giving this necessary specialty only $30,122 of funding per OBGYN resident/fellow. In comparison,

pediatrics received $80,246 per resident/fellow (Rice et al., 2020). With fewer developing scientists and doctors in areas that need it, a vicious cycle is created where less research is done in specialized areas that need it, continuing to affect the development of drugs, medications, and methods of treatment and diagnosis.

Misdiagnosis and its Connection to Gender

As it's now been established, there are issues with funding as it relates to gender, not just because gender was not required to be a variable in research until recently but also because in general, funding tends to favor males. This lack of funding has serious implications due to the lack of necessary research which in turn has large effects on how patients are diagnosed (or misdiagnosed) in the clinical setting. Misdiagnosis is a common experience for women. So much so that a syndrome has been created called the "Yentl Syndrome". This is a term used to describe the misdiagnosis and underdiagnosis of ischemic heart disease in females and the effects of this wrong diagnosis. Ischemic heart disease is a heart disease that as of 2020, globally affected approximately 1,655 individuals per 100,000 (about 1.72% of the global population). This rate of occurrence is expected to exceed 1,845 individuals per 100,000 by 2030 (Khan et al., 2020). Ischemic heart disease, also known as coronary heart disease, is the term for heart problems that are caused by narrow arteries that restrict the amount of blood the heart receives and therefore restrict the body's oxygen intake. This can be caused by naturally having narrow arteries, having a blood clot, or the buildup of plaque along the arterial walls that block the movement of blood (Criteria, I. of M. et al., 2010). When the movement of blood is completely blocked, a myocardial infarction (commonly referred to as a heart attack) occurs. Women under the age of 50 years old are twice as likely to die of a myocardial infarction compared to men of the same

age (Khan & Basnet, 2021). This is because premenopausal women display different heart attack symptoms than men. When coming into the emergency room, women often show signs of discomfort, not in their chest and left arm like men, but in their stomach while also experiencing shortness of breath, nausea, and fatigue. When coupled with other common ailments such as obesity or anxiety, heart conditions are typically dismissed as a side effect of these existing conditions and therefore women are misdiagnosed to be feeling "side effects" instead of being treated for a heart attack. In fact, in medical literature, women's cardiovascular symptoms are often described as "atypical" and "unusual" in literature whereas men's symptoms are explicitly described (McGregor, 2021, p.5). This lack of gender distinction in cardiovascular disease, which the CDC classifies as the leading cause of death for men, women, and people of most racial and ethnic groups in the United States, leads to women being 3 times more likely to die after a heart attack that if properly diagnosed, could have been prevented ("Heart disease facts," 2023).

Yentl syndrome is the most well-known example of misdiagnosis of common diseases in women. When this misdiagnosis occurs, it doesn't just delay diagnosis, it creates a number of unnecessary side effects. Incorrect treatment can be recommended that can potentially exacerbate symptoms while simultaneously prolonging the pain of a heart attack. If a heart attack is not treated in a timely manner, heart cells die and can not be revived, potentially killing the patient. This situation also creates a distrustful relationship between the patient and the doctor as the doctor discounts what their patient is feeling. However, how are doctors supposed to make accurate diagnoses if gender-related differences are unknown? As healthcare research does not take into consideration the differences caused by gender, the differences in pathologies are going

to also remain unknown. This potentially has an unrecognized affect on healthcare and how patients are diagnosed when going to see the doctor. If Yentl syndrome is a common disease affecting large populations of both men and women around the world, it can be extrapolated that there are other diseases that present different symptoms in men versus women. Doctors then misdiagnose and mistreat their patients creating unnecessary additional burden, pain and potential risk of death due to not investing in research to investigate how symptoms have the potential to differ in men versus women.

Mistreatment and its Correlation to Gender in the Drug Development Process

Unrecognized gender differences lead to issues not just in misdiagnosis of diseases but also in mistreatment when it pertains to pharmaceuticals and treatment with drug dosing. A common fact is that men and women metabolize alcohol differently - women at a much faster rate. This is due to a number of factors including differing hormone levels and differing ratio of body fat. How a woman's body metabolizes is also dependent on their menstrual cycle as levels of hormones vary throughout the 28-day cycle. These differing hormone levels don't just have an effect on alcohol breakdown, but also on drug absorption, distribution and excretion (McGregor, 2021, p.72). This means that the same dosage of medication won't affect a man and woman of the same age and weight the same way. Yet despite this knowledge, medications don't have sex-specific dosage recommendations nor are research studies conducted with a sex-based criteria. To counteract this fact, drug companies are including a higher number of women in their phase III studies (human trials). However, because sex is not a factor taken into consideration, many of the results that show differing effects on men and women simply cancel each other out, averaging to reach the "acceptable risk" level deemed by the FDA (McGregor, 2021, p.79).

Additionally, in the earlier stages of clinical studies, in 76% of cases, researchers don't know if they're working with female or male cells. The initial adverse effects observed are therefore not distinguishable by gender as all cells are grouped together. As studies continue, 80% of the specimens used in animal studies are male, causing the baseline observations and potential adverse effects observed and recorded for the human trials to be averaged and then based on a majority male population (McGregor, 2021, p.79). The potential differences in sex are not taken into consideration from the beginning stages of a drug's development. When the drugs are tested in humans, the effects observed and recorded in the studies don't include any potential risks that are specific to one gender versus the other.

Of new drugs being developed, only approximately 7% actually perform sex analysis. Of those studies that do, it has been found that 40% show differences in the pharmacokinetics (drug absorption, distribution, metabolization, and excretion) between genders yet fail to provide different dosage recommendations based on sex (Chu, 2014). Nevermind that tailoring drug dosage based on gender can also increase the safety and efficacy of the drug for everyone as women may require a lower dosage of a medication in order to achieve the same effect as men. Conversely, women, due to hormone fluctuations and differences in body composition, may actually require a higher dosage than men to have the same effect. In 2014, the drug used to treat insomnia, Ambien, gained media attention as the FDA released a report advising women to take 50% of the recommended Ambien dosage (Chu, 2014). This occurred after the FDA received post-market surveillance reports that women ingesting the drug the night before displayed prolonged symptoms of delays in activity, leading to an increase in car accidents while driving the next morning ("FDA approves new label changes and dosing for zolpidem products.," 2017).

Upon further examination, it was found that women eliminate zolpidem, the main ingredient, from their system at a much slower rate compared to men. It is unknown how many drugs should have differing dosages for men versus women and what their effects have been. This type of information most readily comes from reliable sources such as the FDA recall database, and recalls only occur when the effects are negative enough to be consistently reported to the FDA. It shouldn't take the FDA posting an advisory for a distinction to be made between treatment dosage if it can affect not just the efficacy of the drug but the safety of the user as well.

Conclusion

The ramifications of disregarding gender in medicine extend far beyond a simple oversight in healthcare. The effects permeate through the entire industry, from research to diagnosis to treatment, perpetuating a biased male-centric system. Stemming from a historic exclusion of gender in healthcare, the continued disregard for gender differences in healthcare has created a paradigm where critical differences in biology are overlooked. This oversight not only undermines the accuracy and efficacy of medical interventions but also perpetuates the disparities in healthcare outcomes - particularly for women and other marginalized groups. Due to unequal distribution of research funding, scientists and doctors are lacking the critical funds that are needed to propel healthcare forward by hindering advancements and discouraging the specialization of doctors and researchers in fields that need it, due to scarce resources and compensation. This culminates in the harming of patients due to doctors misdiagnosing and mistreating their patients as a result of a lack of necessary knowledge. The consequences of these oversights are profound, leading to unnecessary suffering, increased mortality rates as well as eroding trust between patients and healthcare providers. Addressing these issues requires a

concerted effort from policymakers, healthcare practitioners, researchers, as well as pharmaceutical, biotech and medical device companies. It necessitates a fundamental shift in the approach to biomedical research with a renewed emphasis on inclusivity, diversity and gender sensitivity. It demands the incorporation of gender as a critical variable in all stages of medical research, from study design to clinical trials - regardless of cost - in order to ensure that the research being conducted is tailored to reflect the diverse patient population that it is aiming to help.

Bibliography

Chu, T., PhD in Pharmacology Clinical Lecturer University of California, Riverside School of Medicine Riverside. (n.d.). *Gender differences in pharmacokinetics*. Retrieved March 22, 2024, from https://www.uspharmacist.com/article/gender-differences-in-pharmacokinetics

CDC. (2023, May 15). *Heart Disease Facts | cdc.gov*. Centers for Disease Control and Prevention. https://www.cdc.gov/heartdisease/facts.htm

Criteria, I. of M. (US) C. on S. S. C. D. (2010). Ischemic heart disease. In *Cardiovascular Disability: Updating the Social Security Listings*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK209964/

Epidemiology | presentation and clinical course | healthcare providers | myalgic encephalomyelitis/chronic fatigue syndrome (Me/cfs) | cdc. (2023, March 21). https://www.cdc.gov/me-cfs/healthcare-providers/presentation-clinical-course/epidemiology.html

FDA approves new label changes and dosing for zolpidem products... (2017, December 11). U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and

History of women's participation in clinical research | office of research on women's health. (n.d.). Retrieved March 22, 2024, from https://orwh.od.nih.gov/toolkit/recruitment/history#:~:text=In%201977%2C%20a%20Food%20and,early%20Phase%20II%20drug%20trials.&text=The%20policy%20was%20broad%20and,or%20whose%20husbands%20were%20vasectomized

Khan, B., & Basnet, A. K. (2021). The yentl syndrome: A case report. *JNMA: Journal of the Nepal Medical Association*, *59*(241), 910–912. https://doi.org/10.31729/jnma.7004

Khan, M. A., Hashim, M. J., Mustafa, H., Baniyas, M. Y., Al Suwaidi, S. K. B. M., AlKatheeri, R., Alblooshi, F. M. K., Almatrooshi, M. E. A. H., Alzaabi, M. E. H., Al Darmaki, R. S., & Lootah, S. N. A. H. (2020). Global epidemiology of ischemic heart disease: Results from the global burden of disease study. *Cureus*, *12*(7), e9349. https://doi.org/10.7759/cureus.9349

McGregor, A. J. (2021). *Sex matters: How male-centric medicine endangers women's health and what we can do about it*. Quercus Editions Ltd.

Mirin, A. A. (2021). Gender disparity in the funding of diseases by the u. S. National institutes of health. *Journal of Women's Health*, *30*(7), 956–963. https://doi.org/10.1089/jwh.2020.8682

Rice, L. W., Cedars, M. I., Sadovsky, Y., Siddiqui, N. Y., Teal, S. B., Wright, J. D., Zorbas, A., & Del Carmen, M. G. (2020). Increasing NIH funding for academic departments of obstetrics and gynecology: A call to action. *American Journal of Obstetrics and Gynecology*, *223*(1), 79.e1-79.e8. https://doi.org/10.1016/j.ajog.2020.03.022

The long history of gender bias in medicine. (2021, June 17). TIME. https://time.com/6074224/gender-medicine-history/

Women's health research lacks funding – these charts show how. (2023, May 3). Nature. https://www.nature.com/immersive/d41586-023-01475-2/index.html